REMARKS

This communication is responsive to the issues raised in the Office Action of November 5, 2002. Claims 1-15 remain pending. No new matter has been introduced by this Amendment.

The Office Action

The Abstract was objected to.

Claims 1-15 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 1, 3, 5, 6, and 15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *McIntyre, et al.* (published) in view of *Liotta, et al.* (U.S. Patent No. 5,942,407) and *Weinstein, et al.* (U.S. Patent No. 5,695,930).

Claims 2 and 4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *McIntyre, et al.* (published) in view of *Liotta, et al.* '407 and *Weinstein, et al.* '930 and further in view of *Bjorck, et al.* (U.S. Patent No. 5,965,390).

Claim 7 was rejected under 35 U.S.C. § 103(a) as being unpatentable over *Taliani, et al.* (published) in view of *Liotta, et al.* '401.

Claim 11 was rejected under 35 U.S.C. § 103(a) as being unpatentable over *Chien, et al.* (U.S. Patent No. 6,054,264) in view of *McIntyre, et al.* (published) and *Liotta, et al.* '407.

Claims 12 and 13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Chien, et al.* '264, *McIntyre, et al.* (published), and *Liotta, et al.* '407 further in view of *Bjorck, et al.* '390.

Claim 14 was rejected under 35 U.S.C. § 103(a) as being unpatentable over *Chien, et al.* '264, *McIntyre, et al.* (published), and *Liotta, et al. '407* and further in view of *Weinstein, et al.* '930.

Objection to the Abstract

The Abstract was objected to for being too long.

Applicants have amended the Abstract by deleting the entire second paragraph. As such, withdrawal of the rejection is made.

Response To Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-15 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In rejecting the claims, the Examiner noted a number of issues concerning claims 1, 2, 6-8, 10-12, 14, and 15.

In response to the rejections based on indefiniteness under 35 U.S.C. § 112, second paragraph, Applicants have made a number of amendments to the claims. Applicants submit that the amendments made to the claims address the issues raised by the Examiner without raising any new matter issues.

With respect to claims 1, 7, 11, and 15, Applicants have amended the claims as suggested by the Examiner.

Claims 2, 8, and 12 have been amended to recite that the labeling molecule is a non-antibody molecule which tags all classes of antibodies for subsequent detection. These claims do not add an additional step. Rather, these claims further define the labeling molecule of step (b) in the claim from which they depend.

Claim 6 has been amended (along with a respective paragraph in the specification) to recite that the term AP is "alkaline phosphatase". Applicants submit "AP" is an art recognized abbreviation for alkaline phosphatase. See, for example, *Weinstein, et al.* (U.S. Patent No. 5,695,930) cited in the rejection under 35 U.S.C. § 103(a). As such, inclusion of the term "alkaline phosphatase" in the disclosure introduces no new matter as it merely described the abbreviation "AP".

The Examiner's concern with respect to claims 7-10 being "confusing" is intriguing. In particular, the Examiner states that:

> "Practicing the claims 8-10 as recited would result in labeling all antibody classes, not just IgA as recited in claim 7, making it entirely unclear what method Applicant intends to claim."

(See Office Action of November 5, 2002 at page 4).

In response thereto, Applicants submit that all antibody classes <u>are</u> labeled. It is through the novel use the selective affinity matrix that the immobilized HCV peptide antigens <u>selectively</u> bind to the labeled anti HCV molecules. These bound and labeled anti HCV molecules are what is detected and measured to signify the presence of HCV.

In view of the above, Applicants submit that the claims are clear and definite within the meaning of 35 U.S.C. § 112, second paragraph. Withdrawal of the rejections under 35 U.S.C. § 112, second paragraph are respectfully requested.

Response To Rejections Under 35 U.S.C. § 103(a)

The Examiner has made a number of rejections under 35 U.S.C. § 103(a). A common thread to each rejection is the teaching of *Liotta, et al.* (U.S. Patent No. 5,942,407). In each rejection, the Examiner relies on *Liotta, et al.* for teaching the flow through affinity matrix for selectively detecting labeled anti-HCV peptides.

The invention disclosed is a means to detect antibodies against HCV using oral fluid as a sample medium. Assays in the prior art have not achieved the sensitivity and specificity required to rapidly screen HCV infection in human oral fluid. Most critically, the use of a labeled detection molecule that recognizes all classes of immunoglobulins enhances the ability to detect anti-HCV in oral fluid in an ELISA format or using a flow through system. When detecting anti-HCV using a labeled detection molecule that recognizes only anti-HCV of the IgG class, detection sensitivity was vastly reduced. The incorporation of a detection method that labels multiple classes of anti-HCV, on the other hand, allows for increased detection sensitivity of samples that would otherwise be scored negative using a detection method that only recognizes IgG.

By coupling this detection method to an assay that utilizes a membrane with immobilized HCV peptide antigens present as a trapping zone, followed by subsequent flow of sample through the trapping zones and selective binding of labeled antibodies specific for HCV epitopes within the trapping zone, an immunoassay for the detection of anti-HCV can be performed in a short time period (<15 minutes). The ability to use oral fluid as a sample is of great value to such a rapid diagnostic tool since oral fluid can be collected rapidly and used immediately following collection. An assay using oral fluid, performed on a miniature test platform, analyzed in a small light gathering machine, and able to be completed within 15 minutes from start to finish would be of enormous value as a screening agent for HCV in the population. By decreasing the time of the assay and eliminating the need for invasive blood-based sample acquisition, such an assay would certainly increase the ability to screen, detect and monitor HCV within the population.

The use of an assay to detect anti-HCV in saliva would also be of benefit in the rapid and non-invasive detection of antibodies following vaccinations and monitoring of vaccination efficacy over time, monitoring therapeutic response of patients to treatment regimes and screening for early infection, (as IgA antibodies are known to be an important part of the early stages of the immune response.)

The Examiner's comment on page 9 of the Office Action is actually the point Applicants are attempting to make regarding the novelty of the invention. On page 9 of the Office Action, the Examiner states:

> "One of skill in the art would not be motivated to label all classes of antibodies for detection in order to detect IgA."

(See Office Action at page 9, lines 9-11.) This is precisely Applicants' point. According to the invention all antibodies are labelled. It is through the use of the flow through affinity matrix, which contains immobilized HCV peptide antigens that the labeled anti-HCV molecules are selectively captured (if present in the sample) and detected via the label. The remaining labeled antibodies which are not anti-HCV molecules pass through the matrix. As the Examiner states, no motivation exists for labeling all antibodies in a sample. As discussed above and throughout the specification, it is through the use of a labeled detection molecule that recognizes all classes of immunogens (immunoglobulins) that an enhanced ability to detect anti-HCV in oral fluid is achieved using the flow through affinity matrix. The fact that IgG may also be present is irrelevant to the claimed invention. Detection of IgA is what is critical and is difficult to achieve using prior art methods.

In view of the above, Applicants submit that there is simply no motivation found in the art to label all antibodies in an oral sample and selectively capture and detect only labeled anti-HCV molecules in a flow through affinity matrix. As such, the rejections are deemed improper and should be withdrawn.

CONCLUSION

Applicants believe that this communication addresses all issues raised by the Examiner and places the application in condition for allowability. Reconsideration and notification of allowability are earnestly solicited. The Examiner is encouraged to contact the undersigned should any issues remain.

Respectfully submitted,

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Certificate of Mailing Under 37 CFR 1.8

I hereby certify that this **Amendment and Response Under 35 U.S.C. § 1.111** in connection with **Application Serial No. 09/938,131** is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, BOX AMENDMENT, Washington, D.C. 20231 on this 5th day of February, 2003.

Caroline A. Schweter

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VERSION OF SPECIFICATION, CLAIMS AND ABSTRACT WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph beginning at page 10, beginning at line 8 with the following revised paragraph:

The HCV immunoassay consists of a single nitrocellulose strip with a mixture of recombinant HCV antigens immobilized in a trapping zone 2.4 cm from the top edge of the strip. The nitrocellulose strip is held stationary within a custom-made plastic cassette assembly (FIG. 2A). Oral fluid sample and [AP]alkaline phosphatase (AP)-conjugated goat anti-human IgG+IgM+IgA antibody cocktail are added to the conjugate hinge (FIG. 2B) creating a complex of anti-HCV bound by anti-human-AP antibodies. Alternatively, Protein LA conjugated to alkaline phosphatase can be used as the detection molecule. The hinge is then closed and pressed onto the nitrocellulose test strip for 5 seconds. 60 µl of chase solution is then added to a port on the top of the cassette located just above the hinge region (FIG. 2C) facilitating the migration of sample complex down the nitrocellulose test strip toward the trapping zone while simultaneously washing unbound conjugate antibody through the trapping zone to the bottom wick to prevent non-specific enzyme luminescence within the trapping zone. Upon reaching the trapping zone, the anti-HCV antibody present in the anti-HCV/anti-human-AP complex binds its cognate antigen, thus ceasing its migration. Dried AP substrate is suspended above the trapping zone (FIG. 2A) on a piece of gelbond preventing the substrate from coming into contact with the anti-HCV/anti-human-AP complex in the trapping zone until the cassette is inserted into the luminometer. Four minutes after the addition of the chase solution, the test cassette is inserted into the luminometer. A lever on the back of the cassette is depressed by the luminometer (FIG. 2D) bringing the substrate into contact with the anti-HCV/anti-human-AP complex in the trapping zone, thus initiating the luminescence-generating reaction. Luminescence is measured through the window in the top of the cassette for 1 minute.

In the Claims:

Please replace claims 1, 2, 6, 7, 8, 10, 11, 12, 14, and 15, with the following revised versions thereof:

1. A method for screening for HCV exposure in humans that utilizes an immunoassay for detection of molecule(s) capable of recognizing multiple classes of anti-HCV molecules simultaneously in oral fluid or other bodily fluid samples comprising the following steps:

(a) obtaining a sample of oral fluid or other bodily fluid;

(b) [introduction of] introducing a labeling molecule to label human antibodies present in oral fluid or other bodily fluid samples thereby forming a labeled fluid;

(c) [introduction of] introducing the labeled fluid into a flow through affinity matrix [comprised of] comprising immobilized HCV peptide antigens;

(d) selectively capturing and detecting labeled antibodies which are specific for the HCV peptide antigens [peptides] present within a trapping zone of the flow through affinity matrix,

(e) measuring the binding reaction between the human antibodies and HCV peptide antigens of the trapping zone by amplified enzymatic reaction wherein the presence of a binding reaction between human antibodies and peptide antigens indicates HCV exposure.

2. (Amended) A method according to claim 1 that utilizes a non-antibody molecule as a labeling molecule in step (b) to tag all classes of antibodies [with a reporter molecule] for subsequent detection.

6. (Amended) The method according to claim 1 wherein the labeling molecule is [AP] alkaline phosphatase (AP)-conjugated goat anti-human IgG+IgM+IgA antibody cocktail.

7. (Amended) A method for screening oral fluid samples for the presence of anti-HCV molecules of the IgA class comprising the steps of:

(a) obtaining a sample of oral fluid;

(b) [introduction of] introducing a labeling molecule to the oral fluid to label antibodies in said fluid thereby forming a labeled fluid;

(c) [introduction of] introducing the labeled fluid into a flow through affinity matrix [comprised of] comprising immobilized HCV peptide antigens;

(d) [selective capture] selectively capturing of labeled antibodies which are specific for the [peptides] HCV peptide antigens present within a trapping zone of the flow through affinity matrix;

(e) [detection of] detecting anti-HCV molecules of the IgA class that [require] specifically bind at least one epitope of the HCV [peptides] peptide antigens present within the trapping zone.

8. (Amended) A method according to claim 7 that utilizes a non-antibody molecule as a labeling molecule in step (b) to tag all classes of antibodies [with a reporter molecule] for subsequent detection.

10. (Amended) The method according to claim 7 wherein the labeling molecule of step (b) is [AP] alkaline phosphatase (AP)-conjugated goat anti-human IgG+IgM+IgA antibody cocktail.

11. A method for determining the genotype of HCV virus in a patient having HCV by measuring patient antibody binding to HCV peptides of specific HCV genotypes comprising the steps of:

(a) obtaining a sample of oral fluid or other bodily fluid;

(b) [introduction of] introducing a labeling molecule to label antibodies present in oral fluid or other bodily fluid samples thereby forming a labeled fluid;

(c) [introduction of] introducing the labeled fluid into a flow through affinity matrix [comprised of] comprising immobilized HCV peptide antigens;

(d) selectively capturing and detecting labeled antibodies which are specific for the [peptides] HCV peptide antigens present within a trapping zone of the flow through affinity matrix;

(e) measuring the binding reaction between the human antibodies and HCV peptide antigens of the trapping zone by amplified enzymatic reaction to determine the genotype of HCV virus.

12. (Amended A method according to claim 11 that utilizes a non-antibody molecule to as a labeling molecule in step (b) tag all classes of antibodies [with a reporter molecule] for subsequent detection.

14. (Amended) The method according to claim 11 wherein the labeling molecule is [AP] alkaline phosphatase (AP)-conjugated goat anti-human IgG+IgM+IgA antibody cocktail.

15. (Amended) A kit for use in the method of claim 1 comprising:

(a) a labeling molecule to label antibodies present in oral fluid or other bodily fluid samples;

(b) a flow through affinity matrix [comprised of] comprising immobilized HCV peptide antigens.

In the Abstract:

Please replace the original Abstract with the revised version thereof:

A method and device to detect Hepatitis C (HCV) antibodies in oral fluid is provided. This method introduces a non-antibody detection molecule that labels all classes of patient antibodies in oral fluid, followed by the specific concentration of labeled anti-HCV antibodies by selective capture in a trapping zone consisting of peptide antigens derived from the HCV genome. Signal generated by the labeled antibodies present in the trapping zone is proportional to the number of anti-HCV antibodies bound to the antigens present in the trapping zone. Presence of signal derived from the capture of antibody/detection molecule complexes in the trapping zone is indicative of past exposure to HCV.

[Previous attempts to utilize oral fluid to screen for HCV exposure have been largely unsuccessful, likely due to the vastly decreased levels of antibody present in the oral fluid compared to serum- or plasma as well as the inability to detect other classes of anti-HCV than IgG. A method capable of utilizing oral fluid as an alternative to serum or plasma provides many advantages over traditional blood-based analyses. Oral fluid collection is rapid and non-invasive and eliminates the risks of needle exposure. Oral fluid can be collected by non-medical personnel, relieving health care professionals of the time-consuming and economic burden of obtaining serum samples. Furthermore, oral fluid-based assays may prove to be the preferred method of testing for infants, young children and in developing nations, as well as for patient groups where blood collection is difficult, such as intravenous drug, users, that constitute a significant portion of total HCV cases.]